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Response

Implementing values-based governance for a new bioresource model

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We are pleased to be given the opportunity to read and respond to the peer commentaries on our 'regulatory soup' essay[1] by Bartha Knoppers[2] and Shawn Harmon.[3] Knoppers frames her response as a dichotomy between regulation and collaboration, and emphasizes the role of patient/participant/public engagement as the key to ensuring that precision medicine and its associated infrastructure operates appropriately. In contrast, Harmon focuses on regulatory tools that may be employed to ensure that 'innovations are timely, widely affordable, safe, and effective'. In particular, he draws attention to the

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1 Dianne Nicol et al., *Precision Medicine: Drowning in a Regulatory Soup*?, 3 J. L. & Biosci. 281 (2016).

2 Bartha M. Knoppers. *Precision Medicine: A Matter of Regulation or Collaboration*?, 3 J. L. & Biosci. 687 (2016).

3 Shawn H. E. Harmon, *Modernizing Biomedical Regulation: Foresight and Values in the Promotion of Responsible Research and Innovation*, 3 J. L. & Biosci. 680 (2016).

ways in which 'responsible research and innovation'[4] and 'legal foresighting'[5] can be used as tools for developing 'values-based regulation'.[6]

Both peer commentaries focus particularly on biobanking and data sharing. Here we reflect on developments in this field since 'regulatory soup' was written. We pay particular attention to our work with colleagues at the Centre for Law and Genetics at the University of Tasmania, Australia and our collaborative endeavors with like-minded scholars in other jurisdictions, some of whom also co-authored the regulatory soup essay. Coincidentally our work incorporates many of the ideas expressed in both peer commentaries, with a particular focus on collaborative engagement, identification of values, reflexivity and evidence-based review. We end with a practical example of how we have used these values-based approaches to create a governance framework for a new type of bioresource in Tasmania.

It could well be argued that biobanking and data sharing raise no new regulatory concerns requiring new responses. UK Biobank and its equivalents have been around for a decade and more, and their establishment was premised on having robust ethical and governance frameworks in place from the outset. One of the triggers for our recent research is the questions that are being raised about the ongoing viability of these types of biobanks and whether the governance arrangements that have been developed impose impossible obligations. Underutilization of stored tissue samples has been a surprise to many, as has the demise of some seemingly well-established and well-funded biobanks.[7] On reflection, however, this could have been predicted. We have learned much from the early biobanks and models for biobank governance. Here, we list three key issues relating to tissue and data collection and governance, drawn from our own experience, anecdotal conversations and reports in the academic literature.

i. Tissue collection. Many of the early biobanks aimed to collect a multitude of different types of tissues including fresh frozen tissue, serum, plasma, whole blood, and other more specific tissue types. Additionally, some of the tissues required specialized processing, including the development of tissue microarrays. The more diverse the types of tissues collected and more complex processing required, the larger the laboratory team required to fulfil operational needs. This led to a call for biobanking collection procedures to be embedded within pathology departments to better streamline consent and permit processing procedures to preserve the integrity of tissues. However, this raised challenges for pathology staff in balancing the demands of providing clinical and research services and conducting these additional activities when already operating on limited budgetry resources.[8]

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4 Richard Owen, Phil Macnaghten & Jack Stilgoe, *Responsible Research and Innovation: From Science in Society to Science for Society, With Society*, 39 Sci. & Pub. Pol'y. 751 (2012).

5 Graeme Laurie, Shawn H. E. Harmon & Fabiana Arzuaga, *Foresighting Futures: Law, New Technologies and the Challenges of Regulating for Uncertainty*, 4 L. Innovation & Tech. 1 (2012). See also the various references in Harmon, *supra* note 3, at 682.

6 See particularly Harmon, *supra* note 3, at 684–686.

7 Neil Stephens & Rebecca Dimond, *Closure of a Human Tissue Biobank: Individual, Institutional, and Field Expectations during Cycles of Promise and Disappointment*, 34 New Genet. & Soc. 417 (2015).

8 For examples, see Monya Baker, *Building Better Biobanks*, 486 Nature 141 (2012).

ii. Data collection. Many biobanks also collected general health data from participants. These datasets initially proved useful for early studies, but were limited to the health information provided at the time. Some, but not all anticipated longitudinal follow-up. However, participants who subsequently became unavailable for follow-up, for reasons including death, disinterestedness, loss of contact or whatever else, limited the value of these datasets for longitudinal applications. Longitudinal data collection is also expensive and an ongoing burden on the finances of biobanks.

iii. Governance. Complex governance, consent and operating frameworks instigated to inspire community confidence and encourage community participation could turn out to be expensive to maintain, difficult to fulfil in terms of promised obligations to participants, and challenging in terms of adherence to community concerns over private investment in face of an expectation that biobanks should become self-sustainable.[9]

All of the above resulted in difficulties in reaching recruitment targets, inability to demonstrate broad utility of the samples collected, and lack of widespread uptake. Early cost recovery models were prohibitively expensive and restrictive material transfer agreements (MTAs) reduced the ability of researchers to readily access materials on terms that gave them freedom to do the research and engage with the collaborators of their choice.[10] There was concern that biobanks were 'staggeringly expensive' to operate, and this, together with the need to secure ongoing funding commitments, was always likely to threaten their survival in the long run.[11]

In 'Has the Biobank Bubble Burst', describes three waves of biobanking that have resonance with Knoppers' 3 Rs: establishment of biobank governance and management frameworks; moves toward collaboration and standardization; and recognition of a need to develop new business methods to ensure sustainability. The paper goes on to identify various recurring themes that need to be tackled for future sustainability. In summary, these include consent requirements; ongoing connection with participants; properly maintaining tissue storage; responding to rapidly changing technology; and funding sustainability. Despite the challenges, biobanks continue to offer rich resources for biomedical research, provided that the genomic and other data they generate can be made broadly available.

Several technological and administrative advances in recent times have addressed some of these issues:

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[9] We discuss community concerns relating to commercial involvement in biobanking in Dianne Nicol et al., *Understanding Public Reactions to Commercialization of Biobanks and Use of Biobank Resources*, Soc. Sci. & Med. (2016) doi: 10.1016/j.socscimed.2016.06.028.

[10] Marco Capocasa et al., *Samples and Data Accessibility in Research Biobanks: an Explorative Survey*, PeerJ. (2016) doi: 10.7717/peerj.1613.

[11] See Don Chalmers et al., *Has the Biobank Bubble Burst? Withstanding the Challenges for Sustainable Biobanking in the Digital Era*, BMC Med. Ethics (2016) doi: 10.1186/s12910-016-0124-2, including attribution of the phrase 'staggeringly expensive' to Hank Greely.

i. Advances in available technologies for tissue collection and storage. The imperative of balancing participant needs with minimizing costs and maximizing convenience and utility has driven technological advances. For example, methodologies have been developed that permit routinely collected and archived fixed paraffin-embedded tissues to be used for broader purposes, including the use of next-generation sequencing technologies.

ii. More selective tissue collection. The recognition that tissue samples are expensive to collect and process and the absence of an integrated collection program in pathology departments has led to a re-evaluation of what should be collected. Depending on the circumstances, it may be more appropriate to choose the types of samples to be collected on a project by project basis rather than employing a blanket rule that all tissue samples should be collected at all times, irrespective of likely utility or cost.

iii. Improved data linkage. Government investment in health data linkage has largely overcome the need to collect and store comprehensive health information for each of their samples. This means that biobank samples can be linked to relevant health data to answer questions that are tailored to the nature of the data available. This approach reduces the requirement to anticipate all possible future needs, and eliminates duplicate collection and storage of data already held by government or private institutional bodies.

iv. Re-evaluation of cost recovery and MTA terms. Recognition that practices with regard to cost recovery and MTAs were becoming barriers to the wide use of samples in research has led to greater recognition of the value of open sharing and use of simple standard form MTAs.

New approaches to governance are required in order to address these issues, particularly to minimize bureaucracy. At the same time, it is essential to pay due regard to the complex ethical, legal, and social implications and public concerns associated with tissue and data sharing. Legal requirements, institutional and human research ethics obligations, and the need to secure and maintain public trust could all constrain free and open sharing of genomic data and related activities. A range of considerations must be taken into account in tackling this complex issue. Given that genomic data is shared across borders, responses must also consider international dimensions and, where possible, strive for global harmonization without weak links in the regulatory chain. Moreover, regulatory responses must achieve community acceptance and legitimacy; operational effectiveness; and responsiveness to the inevitable changes in data sharing and in the science itself.[12] Rights, responsibilities, and stewardship need to be reviewed in this fluid, changing, and global environment.[13] A balance must be achieved, fostering widespread sharing and innovation on the one hand, but ensuring adequate ethical and

[12] Roger Brownsword, *Regulating Human Genetics: New Dilemmas for a New Millennium*, 12 Med. L. Rev. 14 (2004).

[13] Roger Brownsword, *Rights, responsibility and stewardship: beyond consent*, in The Governance of Genetic Information: Who Decides? (Heather Widdows & Caroline Mullen eds., 2009) ch. 5.

legal protections for individual research participants and patients, their families and communities on the other.

One clear example of an area crying out for a new approach is the process for ethical review of research, which is still based on the one project, one place, and one point in time model.[14] Projects involving sharing of genomic data globally can be delayed by years due to the need for each research team at each institution to obtain ethical clearance. A working group of the Global Alliance for Genomic Health has been considering these issues for the past two years[15] and recently released a draft policy to address ethics review equivalency.[16]

The need for new strategies for public participation is highlighted in the Knoppers paper. Much of her argument is based on longitudinal cohort studies. We put forward a new participatory model in our 'Has the Biobank Bubble Burst' paper. The gist of this model, which we refer to as the 'walking biobank', is that:

> … the research participants themselves serve as the storage units of their genomic material and the researcher, rather than expending limited funds on the infrastructure to maintain specimens in suspended animation, invites participants in a contact database (through dynamic consent models of contact) to 'walk in' to donate tissue or information as required to address a specific research question.[17]

Despite the value of this type of biobank model, it is unlikely to become the norm. Clinicians will continue to maintain biopsy collections, and project-specific collections will remain common. Nevertheless, Knoppers' point regarding cohort studies having always maintained contact with participants to varying degrees is a good one, and highlights potential mechanisms for the types of flexibility, adaptability, and responsiveness we called for in original paper.

In an area of biomedical research like genomics, where it is essential for large numbers of willing participants to engage, particularly for the longitudinal cohort studies mentioned by Knoppers, public trust is vital.[18] To maintain public trust, changes to biobank management and regulatory reform must incorporate appropriate public engagement.[19] We acknowledge the importance of public engagement, and include it as an essential component of our own work, but it is far from the whole story. While the focus on public collaboration and engagement suggested by Knoppers may meet the requirements of ethical research, and sits well at the base of John Braithwaite's regulatory pyramid,[20] it ignores the important role of regulation at the upper part of the pyramid in providing incentives for stakeholders to act in ethical ways (or disincentives to act in unethical ways), and providing redress when things go wrong.

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[14] Edward S Dove et al., *Ethics Review for International Data-intensive Research*, 351 Science 1399 (2016).

[15] David Townend et al., *Streamlining Ethical Review of Data Intensive Research*, 354 BMJ 4181 (2016).

[16] https://genomicsandhealth.org/work-products-demonstration-projects/ethics-review-recognition-policy (accessed February 23, 2016).

[17] Chalmers et al., *supra* note 11, at 10.

[18] Christine Critchley & Dianne Nicol, *Commercialisation of Genomic Research: the Issue of Public Trust* in Tensions and Traumas in Health Law (Ian Freckleton & Kerry Petersen, 2017).

[19] Nuffield Council on Bioethics, Public Participation Should Be at the Heart of Big Data Projects. Report (2015).

[20] John Braithwaite, *The Essence of Responsive Regulation*, 44 UBC L. Rev. 475 (2011).

While essential, there are limits to the utility of public engagement and collaboration: individuals often can't understand the full extent of what they're consenting to. This works as an imperfect control on biobanking and data sharing as individuals may not object to actions harmful to them, or may object to safe actions, undermining public benefit. Moreover, many segments of the population experience 'research fatigue' or the burden of research, curtailing their willingness and capability to participate to the extent outlined by Knoppers. On the other hand, having these options available for those who wish to engage does enhance public trust, as does the transparency and accountability engendered by such an approach.

In answer to Knoppers' titular question, then, we answer not one or the other, but rather appropriate collaboration is essential to effective, responsive, and flexible regulation. This perspective is supported by Harmon's arguments. He extends the utility of this balanced approach through drawing a sensible parallel between the regulatory requirements of precision medicine infrastructure and those necessitated by emerging technologies and innovative medical therapies. Harmon's view of value-based regulation refers to values in two senses:

i. Values about society—well-being, dignity, justice, and autonomy.
ii. Values about science and its governance—integrity, transparency, engagement, and reflexivity.[21]

He concludes, however, that the majority of existing and emerging biobanks fail to adopt a prospective values-based governance strategy.[22] We agree that this demands new and sustained practices for thinking about governance.

An example of how these considerations might be put into practice is provided by ReD TIGER (the Repository of Donations of Tasmanians in Genetic and Epidemiological Research), in which we have been involved as part of the team developing the governance framework. This is a new form of biorepository that takes into account the experiences and limitations of older style biobanks and builds a governance framework based on the types of values identified by Harmon.

In seeking to establish a Tasmanian biorepository, the founders were motivated by a desire to reduce the burden on participants, to make better use of existing resources, to facilitate high-quality research, and to reflect community values. To this end, community engagement was undertaken prospectively and formed the foundation of the governance framework. Survey results and the findings of a deliberative democracy were analysed to identify the key issues that would influence public trust in a Tasmanian biorepository.[23] These included a focus on research that would benefit Tasmanians; community involvement as a formal component of governance; acceptability of commercialization provided it does not hinder research and commercial interests do not control the biorepository.

The sustainability of the biorepository was a significant theme of the discussions within the deliberative democracy events. There was wide acknowledgement that a

[21] Harmon, *supra* note 3, at 685.

[22] *Id*. at 686.

[23] Nicol et al., *supra* note 9; Rebekah McWhirter et al., *Community Engagement for Big Epidemiology: Deliberative Democracy as a Tool*, 4 J. Pers. Med. 459 (2014).

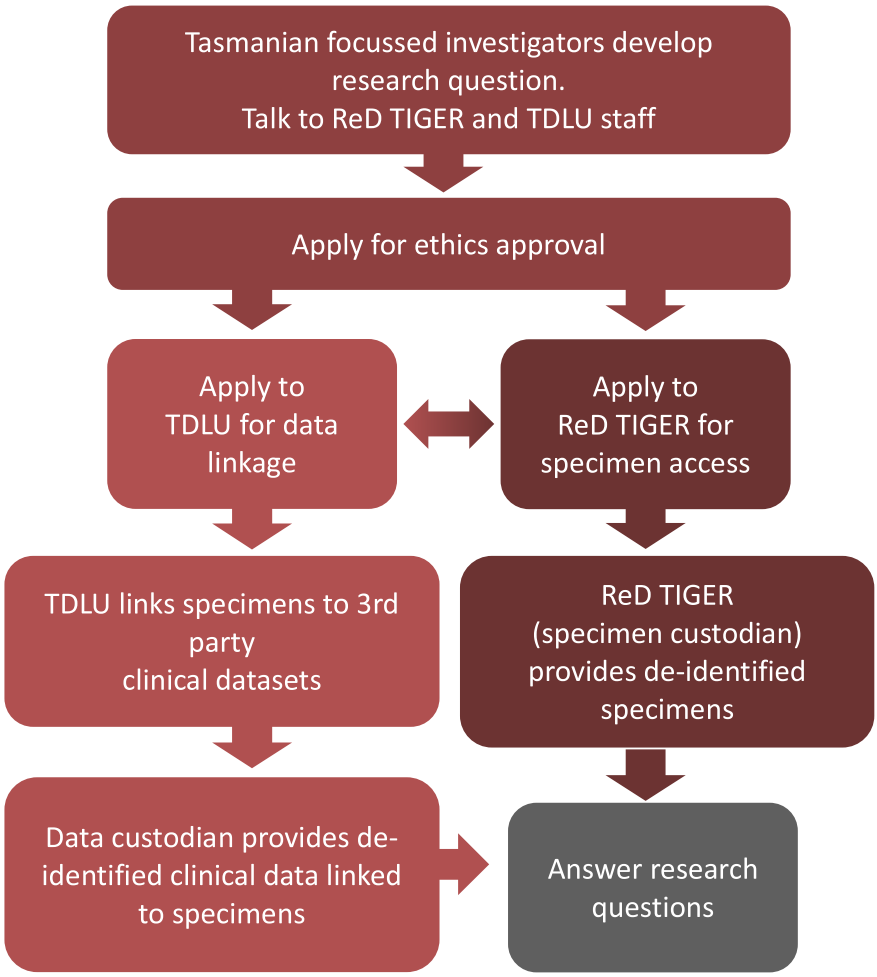

Figure 1. Summary of the ReD TIGER biorepository model.

biorepository that was not economically viable, or that was forced to set unrealistically high cost-recovery charges, would not achieve the aims of facilitating research, reducing participant burden or benefiting the community. This issue, which has plagued previous incarnations of biobanks, was resolved through a radical reconceptualization of what the biorepository should attempt to achieve. Instead of prospective collection, processing and storage of a set range of biospecimens and accompanying data, the proposed ReD TIGER model takes a more efficient and pared down approach, summarized in Figure 1.

The Red TIGER model includes provisions for samples from completed research studies which may be deposited by complying with the consent and ethical review requirements outlined in the governance framework. New studies may utilize the processes, documents, and multimedia consent app developed by ReD TIGER for collection of samples to be deposited at study completion. No data, beyond the minimum necessary for identification, verification of consent, and data linkage, are held

by the repository; all data linkage is undertaken in conjunction with the Tasmanian Data Linkage Unit, providing safe, ethical, and timely access to a broad range of data sources. Data remain with the data custodians, who may be government departments, hospitals, or research studies, among others. This model makes efficient use of research resources, minimizes the burden on participants, and maximizes the potential benefits for the community, while facilitating public trust through meaningful community engagement.

Large-scale biobanking and data sharing are evolving at a rapid pace, and many of the challenges identified by ethical and legal commentators or by early experiences are beginning to be resolved. New challenges will inevitably arise with the emergence of new technologies and developments in social norms, but values-based governance—as demonstrated by the ReD TIGER model—may well prove to be a practical, flexible, and responsive approach for addressing nascent challenges. Public collaboration and engagement are essential components of values-based governance. Just as importantly, regulatory instruments need to be regularly evaluated to ensure their legitimacy, responsiveness, and effectiveness. Whilst creation of new technology-specific laws will rarely be an appropriate response to new technological challenges, changes will be needed if existing laws cannot be applied in ways that reflect societal and scientific values.